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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/060,188	04/14/98	BEHAN	D

HM12/0120

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EXAMINER	
BASI,N	
ART UNIT	**PAPER NUMBER**
1646	12

DATE MAILED: 01/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/060,188	Applicant(s) BEHAN et al
	Examiner Nirmal. S. Basi	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Oct 14, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-44* is/are pending in the application.

Of the above, claim(s) *19-32, 35-38, and 41-44* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18, 33, 34, 39, and 40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Preliminary Amendments filed 10/14/99 and 9/8/99 have been entered.

Election/Restriction

1. Applicant's election of Group I Claims 1-18, 33-34 and 39-40, in Paper No. 11 (1014/99), is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 19-32, 35-38 and 41-44 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Sequence Rules Compliance

2. This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states "reference must be made to the sequence by use of the assigned identifier", the identifier being SEQ ID NO. Sequences in Figure 12 must be identified by their corresponding SEQ ID NO:. Compliance with sequence rules is required.

Specification

The disclosure is objected to because of the following informalities:

Appendices A-D must precede the claims. Appropriate correction is required.

Claim Rejection, 35 U.S.C. 112, second paragrah

4. Claims 1-18, 33-34 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 33, 34 is indefinite because it is not clear what is a partial agonist. Partial agonist is described in the specification as, "ligands which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists". Partial agonist is viewed by the examiner as a relative term which renders the claim indefinite. The term "partial agonist" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since the designation of "partial agonist" is dependent on a comparison with agonist activity, and agonists can effect different degrees of activity, the determination if a compound is a partial agonist can not be made. For example, if two agonists have arbitrary activities of 100 and 50, and the partial agonist has an activity of 75 the determination of the compound being a partial agonist cannot be made.

Claims 1, 33 and 39 are indefinite because it is unclear what is "compound efficacy" and what parameters are measured to determine said efficacy so as to allow metes and bounds of the claims to be determined. Also, the preamble in claim 1 is directed to identifying a candidate compound having activity to an orphan receptor but the body of the claim is directed to a

constitutively activated orphan receptor. Since, orphan receptor and constitutively activated orphan receptor are not the same the claim doe not achieve the goal set forth in the preamble of claim 1. Further, claims 1, 33 and 39 do not recite a final "candidate identification" step achieving the goal set forth in the preamble.

Claims 2, 34 and 40 are indefinite because it is unclear what activity is measured and how it directly identifies if a compound is an inverse agonist.

Claim 14 is indefinite because it is unclear what activity is measured and how it directly identifies if a compound is an inverse agonist. Also claim 14 is indefinite because R and Y are not defined so as to allow the metes and bounds of the claim to be determined.

Claims 3-13 and 15-18 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

35 U.S.C. § 112, first paragraph

5. Claims 1-18, 33-34 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for a method for identifying a candidate compound as a compound having activity selected from the group consisting of inverse agonist activity, partial agonist activity and agonist activity, to an orphan

receptor, non-endogenous constitutively activated G protein coupled cell surface orphan receptor or endogenous constitutively activated G protein coupled cell surface orphan receptor.

The specification suggests strategies to convert G-protein-coupled receptors to become constitutively active after amino acid mutations but provides no examples of orphan receptors which have been converted to constitutively active forms after using said strategies. Orphan receptors by definition are endogenous receptors for which the endogenous ligand specific for that receptor has not been identified or is not known (see page 20, lines 6-7). The specification also refers to orphan receptors and states, "By definition, the orphan receptor has no known ligand, either endogenous or synthetic, which can be used to study the receptor" (page 3, last paragraph). The specification also suggests that constitutively activated G protein coupled cell surface orphan receptors can be used to identify compounds having varying degrees of agonistic activity to said receptors. Binding of ligand to a G protein coupled cell surface orphan receptors results in its interaction with specific G-proteins which inturn results in the activation of various the second messenger G protein couples systems. The methods of instant invention require the production or isolation of constitutively activated G protein coupled cell surface orphan receptors, identifying the G-protein that interacts with said receptor and the trying to determine compounds that bind to said receptors by determining second messenger effects. Watson et al (Ref A) disclose,"Site directed mutagenesis, deletions and chimeric receptor studies have been used in an attempt to identify the region of the β2 adreoceptor that couples with Gs. This work has highlighted a sequence of ~8 amino acids in the N-terminal and ~12 amino acids in the C-terminus of the third

transmembrane loop as important determinants of this interaction. However, it appears that additional regions of the receptor also participate in the binding to the G-protein, most notably in the second intracellular loop, and that it is the overall 3-dimensional structure of the receptor on the cytoplasmic side of the membrane that is important for the interaction with G-protein. It has therefore not been possible to identify consensus amino acid sequences that confer G-protein specificity, and thus G-protein interactions cannot be predicted from the primary amino acid sequence", (page 5, third paragraph). Therefore the disclosure of Watson predicts, using the primary structure of the orphan receptor the skilled artisan cannot predict its associated G-protein. Instant disclosure provides no information on determining specific G-proteins/orphan receptor complexes.

The effect of mutation on proteins is discussed by Rudinger (Ref B). For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification and art as to the effects of specific mutations on specific orphan receptors that lead to constitutive activation of said orphan receptors, the unpredictability in the art of said mutations as disclosed above, what minimal structural requirements are necessary for said function, the lack of known

binding partners of said receptors (G-proteins), would prevent the skilled artisan from practicing the claimed invention without undue experimentation.

No claim is allowed.

Advisory Information

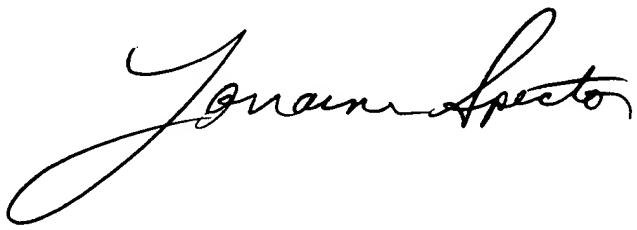
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Thursday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
January 12, 2000



LORRAINE SPECTOR
PRIMARY EXAMINER